chloride, prepared by the addition of a solution of 210 mg. of sodium nitrite in 10 ml. of water to a cold solution of 400 mg. of *p*-nitroaniline in 20 ml. of 1 *N* hydrochloric acid, was added slowly with stirring. The dye was precipitated by the addition of excess water and filtered. Crystallization from 95% ethanol afforded 640 mg. of 11-*p*-nitrophenylazoferruginol, m.p. 163–165°; spectra: infrared (Nujol), C=C 6.22 (m) μ; ultraviolet (methanol), λ_{max} 283 mμ (log ϵ 2.31), 379 (3.97), 479 (2.54); p.m.r., 1-proton singlet at 6.98 p.p.m. (C-14 H), 4-proton multiplet at 8.05 p.p.m. (aromatic hydrogens).

Anal. Calcd. for $C_{26}H_{33}N_3O_3$: C, 71.69; H, 7.64. Found: C, 71.22; H, 7.72.

11-*p*-Nitrophenylazoferruginol Methyl Ether (VIf).—A solution of 435 mg. of VIe and 1.0 ml. of dimethyl sulfate in 100 ml. of dry acetone was refluxed for 18 hr. over 20 g. of anhydrous potassium carbonate. The carbonate was filtered and the solution was evaporated *in vacuo*. Crystallization of the residue from absolute alcohol gave 385 mg. of the azo compound VIf, m.p. 165–167°; spectra: infrared (Nujol), C=C 6.21 (m) μ; ultraviolet (methanol), λ_{max} 281 mμ (log ϵ 3.87), 335 (2.62), 490 (2.09); p.m.r., 3-proton singlet at 3.43 p.p.m. (O-methyl).

Anal. Calcd. for $C_{27}H_{35}N_3O_3$: C, 72.13; H, 7.85. Found: C, 71.97; H, 7.94.

11-Aminoferruginol Methyl Ether (VId).—A mixture of 350 mg. of VIf and 5.0 g. of sodium hydrosulfite in 100 ml. of 95% ethanol was refluxed on a steam bath. Enough water was added to form a homogeneous solution. After 3 hr. the color of the solution changed from blood red to pale yellow. The cooled solution was then poured into an equal volume of water and extracted with three 50-ml. portions of chloroform. The extract was dried and the solvent was removed *in vacuo*. Chromatography of the residual light brown oil, 319 mg., on neutral alumina (activity I) gave 119 mg. of a yellow oil on elution with 1:1 hexane–benzene, whose p.m.r. spectrum was compatible with 11-aminoferruginol methyl ether: 6-proton singlet at 0.98 p.p.m. (C-4 methyls), 3-proton singlet at 1.34 p.p.m. (C-10 methyl), 6-proton doublet at 1.19 p.p.m. (J = 7.0 c.p.s., i-Pro methyls), 1-proton septet at 3.18 p.p.m. (J = 7.0 c.p.s., i-Pro methine), 2-proton multiplet at 2.78 p.p.m. (C-7 methylene), 3-proton singlet at 3.70 p.p.m. (O-methyl), 2-proton multiplet at 3.85 p.p.m. (amino hydrogens), 1-proton singlet 6.35 at p.p.m. (C-14 H).

11-Methoxyferruginol Methyl Ether (Vf).—A solution of 550 mg. of the aldehyde Ve in 8 ml. of diethylene glycol with 0.5 g. of sodium hydroxide and 1 ml. of 90% hydrazine hydrate was heated to 120°. Methanol, 1 ml., was added and the solution refluxed for 10 hr. Water, methanol, and the excess hydrazine hydrate were removed by distillation, and the residue was refluxed for another 8 hr. at 195–205°. The reaction mixture was cooled, diluted with water, and extracted with ether. The extract was dried and the solvent was evaporated. The dark, viscous residue was chromatographed on 15 g. of neutral alumina (activity I). Elution with 20% ether in hexane gave 60 mg. of a white solid. Crystallization from methanol yielded colorless needles of VIf, m.p. 89–90.5°; $[\alpha]^{25}D$ +104° (c 0.13); spectra: infrared (Nujol), C=C 6.24 (w) μ; p.m.r., 3-proton singlet at 1.31 p.p.m. (C-10-methyl).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.78; H, 10.29.

A solution of 119 mg. of VId in 25 ml. of methanol was acidified with 25 drops of concentrated sulfuric acid, cooled to 0–5° in an ice bath and mixed with a solution of 35 mg. of sodium nitrite in methanol. The mixture was allowed to warm slowly to 25° and then was refluxed on the steam bath for 0.5 hr. The cooled solution was neutralized with saturated sodium bicarbonate and extracted with methylene chloride. The extract was dried and the solvent was removed *in vacuo*. A chloroform solution of the residual dark oil was filtered through a short alumina column and the eluted pale yellow oil was distilled. The distillate solidified and was crystallized from methanol yielding 43 mg. of Vf, m.p. 89.5–90.5°; $[\alpha]^{25}D$ +100° (c 0.42); spectra identical with those of Vf above.

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Synthesis of Isoquinolines. I.[1] Copyrine and Isoquinoline Systems Derived from 3-Cyano-4-methylpyridine[2,3]

J. M. BOBBITT AND ROBERT E. DOOLITTLE[4]

Department of Chemistry, The University of Connecticut, Storrs, Connecticut

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3-Cyano-4-methylpyridine was converted to 3-phenylcopyrine and 8-oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline. In the course of the work, an apparently anomalous intramolecular Ritter reaction was observed.

The synthesis of isoquinoline systems from a preformed pyridine nucleus offers numerous possibilities for placing substituent groups in either ring. As part of a continuing effort along these lines, some further reactions of 3-cyano-4-methylpyridine[5] (**1**) have been explored. The ready availability of this compound[5] as well as its two reactive functions make it an attractive starting material for construction of a second ring. Since some fruitless effort had already been expended upon the preparation of an isoquinoline system,[5] it seemed more reasonable to direct this work toward copyrine (2,7-diazanaphthalene). Thus, a copyrine system was realized and even, finally, an isoquinoline system.

The nitrile function was chosen as the first point of attack (Scheme I). Accordingly, **1** was reduced catalytically to 3-(aminomethyl)-4-methylpyridine (**2**) in 84% yield. The formation of secondary amines[6] was suppressed by saturating the solvent with gaseous ammonia. The amine **2** was characterized by two derivatives, a benzamide and an acetamide (**3**). Attempts to convert **3** to the dicyclic product **4** by boiling in acetic anhydride or by treatment with sodium hydride were not successful.

Treatment of the amine **2** with *m*-nitrobenzaldehyde converted it to the imine **5** in 95% yield. An attempt to convert **5** to the dicyclic product **6** by refluxing it with acetic anhydride and sodium acetate was not successful. However, a product was isolated which

(1) This paper represents the beginning of a new series. For our preceding work on isoquinoline alkaloids, see J. M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Letters*, 575 (1963).

(2) This paper was presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963.

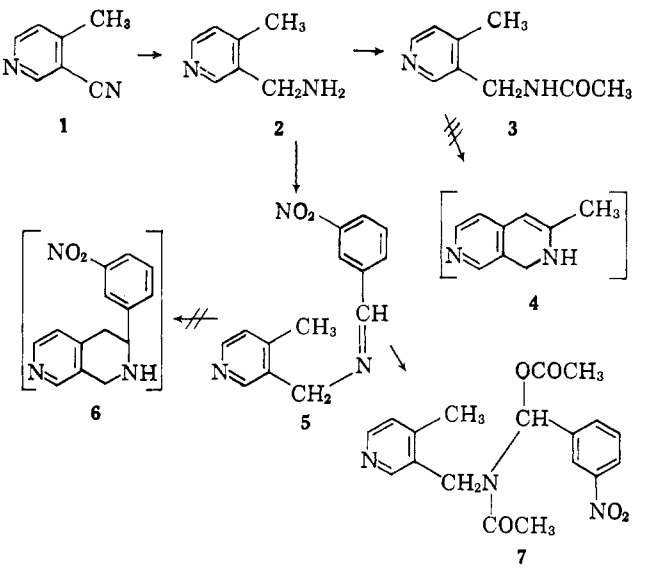
(3) This investigation was supported in part by Research Grant No. CY-3905 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(4) Abstracted in part from the Ph.D. Dissertation of R. E. Doolittle, The University of Connecticut, Storrs, Connecticut, 1963.

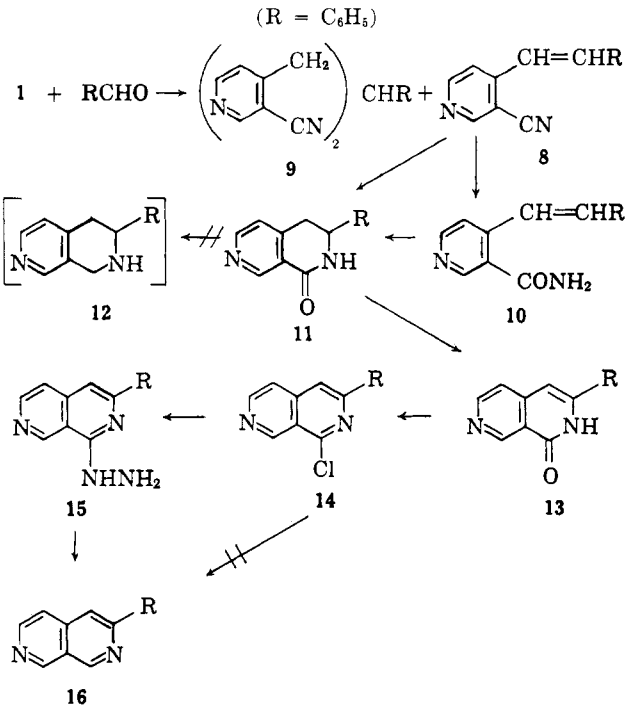
(5) J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960).

(6) H. Adkins and H. I. Cramer, *J. Am. Chem. Soc.*, **52**, 4349 (1930).

SCHEME I



SCHEME II
(R = C_6H_5)



displayed an infrared spectrum of both an acetate and an acetamide. Structure **7** was assigned to this product on the basis of a previously observed[7] reaction of this type.

The methyl group of **1** was chosen next for possible extension to another ring (see in Scheme II). This method, which was finally successful, followed a route similar to, but not identical with, that used by Ikekawa[8] for the synthesis of copyrine and 3-methylcopyrine. Treatment of **1** with benzaldehyde in the presence of acetic anhydride[9] or hydrochloric acid[10] converted it to 3-cyano-4-stilbazole (**8**) in 29 to 40% yield. The low yield was partially due to the formation of a second product, which was formulated as **9** as a result of its analysis and infrared spectrum. Compound **9** clearly arises from further condensation of the stilbazole with starting material. Although the hydrochloric acid reaction gave slightly lower yields of product, it was preferred since less **9** was formed.

The nitrile group of **8** was hydrolyzed with Amberlite IRA-401-OH[5] to produce 3-carbamyl-4-stilbazole (**10**) in 83% yield. Treatment of either the nitrile **8** or the amide **10** with polyphosphoric acid[11] led to the formation of the dicyclic structure, 1-oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (**11**), in yields of 90 to 95%.

The conversion of **8** to **11** in an intramolecular Ritter reaction is in apparent contradiction to several reports[12-15] that unsaturated nitriles do not undergo cyclization to lactams when the ring to be formed is of seven members or less. The usual result is either predominant[15] or total formation of an unsaturated ketone. In the present case, the lactam formation may be attributed to an electron-withdrawing effect that the pyridinium nucleus has on the double bond. This electron deficiency would cause inhibition of the acylation reaction leading to ketone formation and allow the slower lactam formation to occur.

Reduction of the lactam **11** with a large excess of lithium aluminum hydride failed to yield the desired 3-phenyl-1,2,3,4-tetrahydrocopyrine (**12**).

Since the reduction to a tetrahydro system appeared to be difficult, the paths leading to the completely aromatic system were explored. Thus, the aromatization of **11** proceeded smoothly in *p*-cymene with a 10% palladium-on-charcoal catalyst to yield 1-oxo-3-phenyl-1,2-dihydrocopyrine (**13**) in 96% yield. This compound had been prepared previously[16] and formulated as 1-oxo-1,4-dihydrocopyrine. However, structure **13** seems to be more in line with the infrared spectrum. The physical constants of **13** agreed with those recorded.[16]

The amide **13** was converted to 1-chloro-3-phenylcopyrine (**14**) in 75% yield by treatment with phosphorus oxychloride according to the method of Ikekawa.[8] Attempted hydrogenolysis of **14** with palladium chloride or palladium on calcium carbonate led to complex mixtures of partially hydrogenated materials, thus paralleling previous work.[17]

An alternate method[8] involving hydrazinolysis of the chloride and oxidation of the hydrazino derivative was then attempted. The halide **14** reacted readily with hydrazine hydrate in ethanol to yield the relatively unstable 1-hydrazino-3-phenylcopyrine (**15**) in 90% yield. Subsequently, **15** was oxidized to 3-phenylcopyrine (**16**) in 55% yield with cupric sulfate.[8,18] The amine was characterized as a monopicrate and a monostyphnate. The structure of **16** was assigned on the basis of its mode of formation, its analysis, and the similarity of

(7) M. Passerini and M. Pia Macentelli, *Gazz. chim. ital.*, **58**, 641 (1928); *Chem. Abstr.*, **23**, 2951 (1929); J. B. Ekeley, M. C. Swisher, and C. C. Johnson, *Gazz. chim. ital.*, **62**, 81 (1932); *Chem. Abstr.*, **26**, 3239 (1932); A. W. Burgstahler, *J. Am. Chem. Soc.*, **73**, 3021 (1951).

(8) N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 268 (1958); *Chem. Abstr.*, **53**, 372 (1959).

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(10) M.-C. Chiang and W. H. Hartung, *J. Org. Chem.*, **10**, 21 (1945).

(11) R. K. Hill, *ibid.*, **22**, 830 (1957).

(12) R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).

(13) R. T. Conley and M. C. Annis, *J. Org. Chem.*, **27**, 1961 (1962).

(14) R. T. Conley and B. E. Nowak, *ibid.*, **27**, 1965 (1962).

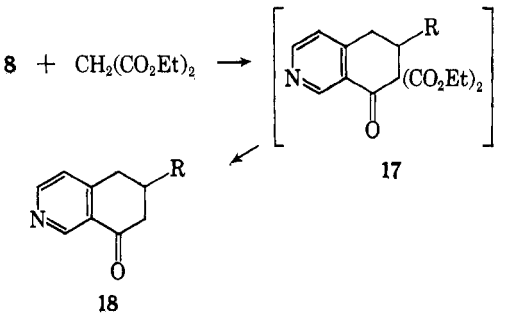
(15) R. T. Conley and R. J. Lange, *ibid.*, **28**, 210 (1963).

(16) F. Krohnke, K. Ellegast, and E. Bertram, *Ann.*, **600**, 198 (1956).

(17) B. M. Ferrier and N. Campbell, *J. Chem. Soc.*, 3513 (1960).

(18) H. E. Baumgarten and H. C. Su, *J. Am. Chem. Soc.*, **74**, 3828 (1952).

SCHEME III
(R = C_6H_5)



its ultraviolet spectrum with that of 2-phenylnaphthalene.[19]

Finally, an isoquinoline system was realized (see Scheme III). Treatment of the stilbazole **8** with ethylmalonate and sodium ethoxide, followed by acid hydrolysis led to the formation of 8-oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline (**18**) in 64% yield. The structure was assigned on the basis of the analysis of **18**, an oxime, a picrate, and a styphnate, and the infrared spectrum (1680 cm.$^{-1}$). The reaction can be envisioned as a base-catalyzed addition of ethyl malonate to the double bond of the stilbazole followed by a Dieckmann-type condensation, hydrolysis, and decarboxylation.

Experimental[20]

Thin layer chromatography[21] was used extensively during this investigation. All analytical samples were examined by this method before analysis. It was used to follow the course and rate of several of the reactions. The areas of the layers containing the products were visualized by either spraying the layer with modified Dragendorff reagent[22] or by examining the layer under ultraviolet light.

3-(Aminomethyl)-4-methylpyridine (**2**).—3-Cyano-4-methylpyridine (**1**, 25 g.) was dissolved in 225 ml. of absolute ethanol which had been previously saturated with gaseous ammonia. Approximately 3 g. (one teaspoon) of W-5[23] Raney nickel catalyst was added and the mixture was shaken in a Parr low-pressure hydrogenator under 50 lb. of hydrogen, until the theoretical quantity of hydrogen had been absorbed (6 hr.). The catalyst was removed by filtration; the filtrate was distilled at atmospheric pressure through a 10 × 1 cm. column equipped with a tantalum wire spiral to remove the ethanol, and the residue was distilled at reduced pressure. The product **2**, 21.5 g. (84%), distilled as a clear liquid, b.p. 63° (0.12 mm.), $n^{22}D$ 1.5492.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.80; H, 8.49; N, 22.81.

The **benzamide** of **2** was prepared by a standard method[24] and had m.p. 111–112.5° (cap.) after four recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.48; H, 6.12; N, 12.08.

3-Acetamidomethyl-4-methylpyridine (**3**).—The acetamide **3** of 3-(aminomethyl)-4-methylpyridine was prepared according to a standard procedure.[24] After four recrystallizations from absolute ethanol, it had m.p. 81–82°.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.12; H, 7.45; N, 16.94.

Attempted Preparation of 3-Methyl-1,2-dihydrocopyrine (**4**). **Acetic Anhydride Method.**—3-Acetamidomethyl-4-methylpyridine (**3**, 0.5 g.) was dissolved in 25 ml. of distilled acetic anhydride and refluxed for 24 hr. The solution was cooled and poured into water. The aqueous solution was made alkaline with sodium carbonate and extracted with chloroform. The chloroform extract was examined by thin layer chromatography using chloroform–ethanol (95:5) as developer and showed only the presence of the starting amide **3**.

Attempted Preparation of 3-Methyl-1,2-dihydrocopyrine (**4**). **Sodium Hydride Method.**—3-Acetamidomethyl-4-methylpyridine (**3**) (0.5 g., 0.00305 mole) and sodium hydride (0.0745 g., 0.0031 mole), as a 25% suspension in mineral oil, were heated under reflux for 8 hr. in 15 ml. of dry *m*-xylene. The mixture was cooled and 15 ml. of water was cautiously added. The layers were separated and the aqueous layer was extracted with 25 ml. of ether. The ether and xylene solutions were combined and examined by thin layer chromatography using chloroform–ethanol (95:5) as developer. Only starting material **3** could be detected.

3-(N-*m*-Nitrobenzylideneaminomethyl)-4-methylpyridine (**5**).—3-(Aminomethyl)-4-methylpyridine (**2**, 24.4 g., 0.2 mole) and *m*-nitrobenzaldehyde (30.0 g., 0.22 mole) were dissolved in 300 ml. of dry benzene. The mixture was heated under reflux, and the water was azeotropically removed with a Dean–Stark water separator. The theoretical amount of water (0.2 mole) was collected in 6 hr. The yellow solution was concentrated under vacuum to give 48.5 g. (95%) of **5**. The imine had m.p. 96.5–97.5° after one recrystallization from 1 l. of heptane–benzene (20:1).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.57; H, 5.08; N, 16.64.

Attempted Preparation of 3-(*m*-Nitrophenyl)-1,2,3,4-tetrahydrocopyrine (**6**).—This is a modification of the method of Shaw and Wagstaff.[9] 3-(N-*m*-Nitrobenzylideneaminomethyl)-4-methylpyridine (**5**, 2.55 g., 0.01 mole), freshly fused sodium acetate (1.64 g., 0.02 mole), and 20 ml. of acetic anhydride were heated under reflux for 1 hr. The mixture was cooled and poured into ice and water. It was made alkaline with sodium carbonate and extracted with chloroform. The chloroform extract was evaporated to give 3.5 g. of a dark yellow oil which was dissolved in benzene and chromatographed over 100 g. of silica gel using benzene–ethanol (20:1) as eluent. Fractions of 10 ml. were collected. Fractions **5** through **8** were shown by thin layer chromatography, using chloroform–ethanol (95:5) as developer, to contain one compound and they were combined. A yellow oil (**7**), 1.3 g., was obtained which showed infrared absorption (thin film) at 1680 (CONHR) and 1760 cm.$^{-1}$ ($OCOCH_3$) (see discussion).

3-Cyano-4-stilbazole (**8**). **Acetic Anhydride Method.**[9]—3-Cyano-4-methylpyridine (**1**, 5.9 g., 0.05 mole), benzaldehyde (5.5 g., 0.052 mole), and 20 ml. of distilled acetic anhydride were sealed in a glass ampoule. The ampoule was heated in an oil bath at 120° for 24 hr., then cooled to −80°, and opened. The contents were poured into 100 ml. of water and ice, and the solution was made alkaline with sodium carbonate and steam distilled to remove unchanged benzaldehyde. The contents of the flask were extracted with chloroform and the chloroform extract was evaporated to a solid residue. This was sublimed at 125° (0.04 mm.) to give 4.1 g. (40%) of **8**. This product was shown by thin layer chromatography, using ether as developer, to contain a slight impurity. An analytical sample of **8** was obtained by using preparative thin layer chromatography with ether as developer. This was followed by five recrystallizations from hexane–benzene (1:1) to give the pure material, m.p.

(19) It has been stated that the replacement of as many as two carbons by nitrogens in an aromatic system does not appreciably change its ultraviolet spectrum; see A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold, Ltd., London, 1957, p. 154.

(20) All melting points were taken on a Kofler micro hot-stage apparatus or in an open capillary tube and are corrected. The infrared spectra, ultraviolet spectra, and refractive indices were taken on a Perkin-Elmer Infracord, Cary-14 recording spectrophotometer and an Abbé refractometer respectively. The microanalyses were performed by H. Frohofer of the Organic Chemistry Institute of the University of Zürich, Switzerland; Geller Laboratories of Bardonia, N. Y.; Drs. Weiler and Strauss, Microanalytical Laboratory, Oxford, England; Microanalytical Laboratory, Brugg, Switzerland. Thin layer chromatography was done on silica gel G (Brinkmann, Westbury, N. Y.) layers, 250 μ thick. Preparative thin layer chromatography was done on silica gel G layers, 1 mm. thick, prepared with a Stahl–Desaga apparatus (Brinkmann).

(21) J. M. Bobbitt, "Thin-Layer Chromatography," Reinhold Publishing Co., New York, N. Y., 1963.

(22) R. Munier and M. Macheboeuf, *Bull. Soc. Chim. Biol.*, **33**, 846 (1951); *Chem. Abstr.*, **46**, 4171 (1952).

(23) H. Adkins and H. R. Billica, "Organic Squtheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176.

(24) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 226.

118–120°; infrared absorption in potassium bromide: 1610 (C=C) and 2205 cm.$^{-1}$ (C≡N).

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.61; H, 4.93; N, 13.45.

The solid **9**, which remained in the sublimation pot, was washed out with ether and gave 3.0 g. of a solid with m.p. 180–181°. This was shown by thin layer chromatography, using ether as developer, to be the same as the impurity in the sublimate of **8**. The analytical sample, after recrystallization from absolute ethanol and sublimation at 150° (0.04 mm.), had m.p. 180–181°; infrared absorption in potassium bromide: 2210 cm.$^{-1}$ (C≡N).

Anal. Calcd. for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.65; H, 4.96; N, 17.39.

3-Cyano-4-stilbazole (8). Hydrochloric Acid Method.[10]—3-Cyano-4-methylpyridine (**1**, 5.9 g., 0.05 mole), benzaldehyde (5.88 g., 0.055 mole), and 7 ml. of concentrated hydrochloric acid were heated under reflux for 2 days. The cooled reaction mixture was treated in exactly the same manner as in the acetic anhydride method. 3-Cyano-4-stilbazole was isolated in 29% yield; however, it was shown by thin layer chromatography, using ether as developer, to contain only a trace of the impurity **9**.

3-Carbamyl-4-stilbazole (10).—Crude 3-cyano-4-stilbazole (**8**, 2.0 g.), 2.0 g. of wet Amberlite IRA-401-OH anion-exchange resin,[5] and 75 ml. of distilled water were stirred and refluxed for 10 hr. The mixture was cooled and filtered. The precipitate, consisting of product and resin, was extracted with boiling ethanol. The ethanol was evaporated under vacuum to yield 1.8 g. (83%) of **10**. The analytical sample, after recrystallization from absolute ethanol, had m.p. 196.5–197.5°; infrared absorption in potassium bromide: 1630 (C=C), shoulder at 1650 cm.$^{-1}$ ($CONR_2$).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.08; H, 5.35; N, 12.29.

1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (11). From 3-Carbamyl-4-stilbazole.—This is essentially the method of Hill.[11] Crude 3-carbamyl-4-stilbazole (**10**, 0.250 g.) and polyphosphoric acid (15.0 g.) were mixed in a 40-ml. test tube. The tube was heated in an oil bath at 135° and stirred vigorously until all the solid had dissolved. The mixture was poured while still hot into 100 ml. of ice and water, and the acid solution was extracted with 25 ml. of chloroform. The acid solution was neutralized with sodium carbonate and the mixture was extracted with chloroform. The chloroform was evaporated to give an oil which solidified upon trituration with dry ether. The solid was sublimed at 150° (0.04 mm.), to give 0.225 g. (90%) of **11**. The analytical sample upon recrystallization from hexane–benzene (1:1) had m.p. 160–162°; infrared absorption in potassium bromide: 1650 cm.$^{-1}$ (CONHR).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.97; H, 5.35; N, 12.16.

1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (9). From 3-Cyano-4-stilbazole.—3-Cyano-4-stilbazole (**8**, 0.5 g.) was heated and stirred with 9.0 g. of polyphosphoric acid in a test tube at 130° until all the solid material had dissolved. The reaction was then treated in the same manner as in the preparation from **10**. This method gave 0.464 g. (90%) of lactam **11**.

Attempted Reduction of 1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (11). With Lithium Aluminum Hydride.—This is essentially the technique used to reduce N-phenylsuccinimide.[25] 1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (**11**, 0.255 g., 0.0011 mole) was placed in the thimble of a micro Soxhlet extractor. A solution of lithium aluminum hydride (0.350 g., 0.0092 mole) in 70 ml. of anhydrous ether was placed in the flask of the extractor. The material was extracted until the thimble was empty (3 days). The suspension was cooled in an ice bath and was hydrolyzed by the method of Amundsen,[26] which involved the addition of 0.4 ml. of water, 0.3 ml. of 20% sodium hydroxide, and 1.4 ml. of water in that order. The suspension was filtered and the precipitated hydroxides were pulverized and extracted several times with ether. The ether extracts and original filtrate were evaporated to give an oil. Thin layer chromatography, using ether as developer, indicated the presence of three products in addition to starting material. Upon repeating the experiment using tetrahydrofuran as solvent, essentially identical results were obtained.

(25) W. G. Brown, *Org. Reactions*, **6**, 492 (1951).

(26) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

1-Oxo-3-phenyl-1,2-dihydrocopyrine (13).—This is a modification of two other procedures.[27,28] 1-Oxo-3-phenyl-1,2,3,4-tetrahydrocopyrine (**11**, 2.0 g.) and 10% palladium-on-charcoal catalyst[29] (0.5 g.) were heated under reflux, with vigorous stirring, in 75 ml. of dry *p*-cymene. The mixture was cooled and filtered. The solid which consisted of charcoal and product was extracted in a Soxhlet extractor with methanol for 3 days. The methanol was evaporated under vacuum to give 1.9 g. (96%) of **13**. The analytical sample after recrystallization from absolute ethanol had m.p. 239–239.5° (cap.), lit.[16] m.p. 237–238°; infrared absorption in potassium bromide: 1620 (C=C), 1650 (CONHR) and 3170 cm.$^{-1}$ (N–H).

1-Chloro-3-phenylcopyrine (14).—This is the method used by Ikekawa.[8] 1-Oxo-3-phenyl-1,2-dihydrocopyrine (**13**, 3.0 g.) and 25 ml. of phosphorus oxychloride were heated to 180° in a sealed ampoule for 24 hr. The ampoule was cooled and opened, and the contents were poured into ice and water. The acid solution was neutralized with sodium carbonate and extracted with chloroform. The chloroform extract was evaporated under vacuum to give a dark oily residue. This was sublimed at 110° (0.04 mm.), yielding 2.44 g. (75%) of white crystalline **14**. The melting point was 128–130° and the sublimed material was used directly for the analytical sample.

Anal. Calcd. for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; Cl, 14.73; N, 11.64. Found: C, 70.20; H, 3.50; Cl, 14.76; N, 11.76.

Attempted Preparation of 3-Phenylcopyrine (16). Using Palladium Chloride.—This is the method used by Bobbitt and Scola[5] for the preparation of **1**. 1-Chloro-3-phenylcopyrine (**14**, 0.048 g., 0.002 mole) was dissolved in 25 ml. of methanol containing 0.2 g. (0.0021 mole) of potassium acetate. Freshly prepared palladium chloride[30] (5.0 mg.) was added and the mixture was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen had been absorbed (2 hr.). The highly fluorescent yellow mixture was filtered, and the filtrate was examined by thin layer chromatography with ether as developer. This indicated the presence of about five products. This mixture was not further investigated.

Attempted Preparation of 3-Phenylcopyrine (16). Using Palladium on Calcium Carbonate.—This is the procedure used by Ikekawa.[8] 1-Chloro-3-phenylcopyrine (**14**, 0.048 g., 0.002 mole) was dissolved in 25 ml. of absolute ethanol and 10 mg. of palladium-on-calcium carbonate catalyst[31] was added and the mixture was subjected to hydrogenation at atmopheric pressure. After 6 hr. the catalyst was removed by filtration and the filtrate was examined by thin layer chromatography using ether as developer. This showed the presence of three products, two of which were a yellow fluorescent color. Consequently, the hydrogenolysis route was abandoned.

1-Hydrazino-3-phenylcopyrine (15).—This is the procedure described by Ikekawa[8] for 1-hydrazinocopyrine. 1-Chloro-3-phenylcopyrine (**14**, 0.200 g., 0.00831 mole) and 85% hydrazine hydrate (5 ml., 5 g., 0.1 mole) were dissolved in 25 ml. of absolute ethanol. The mixture was refluxed for 4 hr., cooled, and diluted with 50 ml. of water. The solution was filtered and the precipitate was washed with water. The hydrazine (**15**, 0.177 g.) was obtained in 90% yield. It had m.p. 214–216° dec. (cap.). A satisfactory analytical sample could not be obtained as the material underwent extensive decomposition upon recrystallization.

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.90; H, 5.14; N, 24.96.

3-Phenylcopyrine (16). From 15.—This is essentially the method of Baumgarten and Su.[18] Crude 1-hydrazino-3-phenylcopyrine (**15**, 0.177 g.) was suspended in 100 ml. of distilled water, stirred, and heated to boiling. Cupric sulfate (0.598 g.) dissolved in 50 ml. of water was added dropwise. Vigorous gas evolution took place. The cupric sulfate solution was added over a period of 2 hr. and the mixture was stirred and refluxed for 2 hr. longer, cooled, and made strongly alkaline with 20% sodium hydroxide. The gelatinous mixture was continuously extracted with ether for 24 hr. The ether was evaporated under vacuum and the crystalline residue was purified by preparative

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(30) F. P. Treadwell and W. T. Hall, "Analytical Chemistry," 9th Ed., John Wiley and Sons, Inc., New York, 1955, p. 525.

(31) A. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1959, p. 167.

thin layer chromatography using ether as the developer. The band containing the product could be seen readily under ultraviolet light. This was scraped off, and the product was extracted from the silica gel with chloroform in a Soxhlet extractor. The chloroform was evaporated and the residue was sublimed at 100° (0.04 mm.) to give 0.086 g. (55%) of pure material with m.p. 126–128°; infrared absorption in potassium bromide: 1610 cm.$^{-1}$ (aromatic); ultraviolet absorption in 95% ethanol (max.): 295 mμ (log ε 3.96), 254 (4.34), and 230 (4.05); ultraviolet absorption spectrum of 2-phenylnaphthalene in 95% ethanol (max.)[32]: 288 mμ (log ε 4.1), 259 (4.1), and 251 (4.8).

Anal. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.76; H, 4.81; N, 13.59.

A **monopicrate**, m.p. 210–211°, was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{20}H_{13}N_5O_7$: C, 55.18; H, 3.01; N, 16.09. Found: C, 55.19; H, 3.18; N, 16.06.

A **monopicrolonate**, m.p. 255–256° dec. (cap.), was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{24}H_{18}N_6O_5$: C, 61.27; H, 3.86; N, 17.87. Found: C, 61.13; H, 3.95; N, 18.19.

8-Oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline (18).—Sodium (287.5 mg., 0.0125 g.-atom) was dissolved in 35 ml. of anhydrous ethanol. Ethyl malonate (2.0 g., 0.0125 mole) was added, followed by 2.060 g. (0.01 mole) of 3-cyano-4-stilbazole (**8**). The red solution was stirred for 8 hr. at room temperature. Subsequent examination by thin layer chromatography, using ether as developer, showed the absence of any starting material. The ethanol was evaporated under vacuum and the oily red residue was heated under reflux for 6 hr. with 60 ml. of 3 *N* hydrochloric acid. The cooled acid solution was extracted once with 25 ml. of ether, made slightly alkaline with solid sodium bicarbonate, and extracted six times with 35-ml. portions of chloroform. The combined chloroform extracts were dried over magnesium sulfate. The chloroform was evaporated to give 2.5 g. of oil. The oil was dissolved in ether, evaporated on 5 g. of deactivated neutral alumina, and chromatographed on 100 g. of neutral alumina, activity grade IV (Brockmann). The column was developed using gradient elution. The first solvent was 1 l. of *n*-pentane followed by 1 l. of ether–*n*-pentane (25:75), followed by 1 l. of ether–*n*-pentane (40:60). Fractions of 15 ml. were collected and examined by thin layer chromatography using ether–*n*-pentane (75:25) as the developer. Fractions **1–72** contained nothing. Fractions **73–80** contained an impurity. Fractions **81–100** contained impurity and a trace of the product. Fractions **101–150** contained pure product. The latter were combined and evaporated to yield 1.433 g. (64% yield) of 8-oxo-6-phenyl-5,6,7,8-tetrahydroisoquinoline (**15**). After sublimation (110° at 0.04 mm.) and three recrystallizations from benzene–hexane (1:1), the ketone had m.p. 83–84°; infrared absorption in potassium bromide: 1680 cm.$^{-1}$ (ArCO—).

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.93; H, 5.91; N, 6.37.

An **oxime**, m.p. 228–229° (cap.), was prepared in aqueous ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.34; H, 6.06; N, 11.71.

A **picrate**, m.p. 154–157° (cap.), was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{21}H_{16}N_4O_8$: C, 55.76; H, 3.57; N, 12.38. Found: C, 55.84; H, 3.70; N, 12.39.

A **styphnate**, m.p. 190–191° (cap.), was prepared in ethanol and recrystallized from the same solvent.

Anal. Calcd. for $C_{21}H_{16}N_4O_9$: C, 53.85; H, 3.44; N, 11.96. Found: C, 53.80; H, 3.60; N, 12.03.

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Thio Sugars. III. Synthesis and Rearrangement of 2-(3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea Dihydrobromide and Analogs[1]

M. L. WOLFROM, W. A. CRAMP, AND D. HORTON

Department of Chemistry, The Ohio State University, Columbus 10, Ohio

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Condensation of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-galactopyranosyl bromide hydrobromide (I) with thiourea in acetone solution gave 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranosyl)-2-thiopseudourea dihydrobromide (II) crystallizing with 1 mole of acetone and further characterized as the diflavianate; condensation in a 2-propanol medium gave predominantly isopropyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-galactopyranoside hydrobromide (IV). Improved preparative directions are cited for the D-*gluco* analog (V) of II and it is shown that some isopropyl tetra-*O*-acetylglycoside is likewise formed when V is prepared in 2-propanol solution. Substance V was further characterized as its diflavianate. Substance II, an analog of the radiation protective agent 2-(2-aminoethyl)-2-thiopseudourea (AET), undergoes rearrangement in neutral solution to 3,4,6-tri-*O*-acetyl-2-deoxy-2-guanidino-1-thio-β-D-galactose hydrobromide (III). Determination of III and its D-glucose analog (VI) by thiol assay is described.

In the first paper[2] in this series we reported the preparation of 2-(3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl)-2-thiopseudourea dihydrobromide (V), and a subsequent paper[3] described the rearrangement undergone by V at pH 7 in aqueous solution to give 3,4,6-tri-*O*-acetyl-2-deoxy-2-guanidino-1-thio-β-D-glucose (VI). Systems of this type are of interest as potential radiation protective agents, since they incorporate into a carbohydrate matrix the functional groups of 2-(2-aminoethyl)-2-thiopseudourea (AET). The latter[4] is one of the most effective agents known for the protection of biological systems against ionizing radiation,[5] but its high toxicity is a disadvantage. It was hoped that carbohydrate derivatives would function as protective compounds with low toxicity. The present work describes the synthesis of the D-galactose analog (II) of V, together with further studies on V. A study of the rearrangement of II and V to the corresponding guanidino thiols (III and VI) is also described. It was considered that the D-galactose derivative (II) would be less readily metabolizable than the D-glucose analog

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